

BS

# MS Contin is Unequalled...

■ Unequalled  
Bioavailability...

Unequalled  
Effectiveness...

Unequalled  
Experience...

**MS Contin®**   
(morphine sulfate 30 mg  
controlled-release) tablets

**Trial Exhibit**

*Purdue et al. v. Endo et al.*  
Nos. 00 Civ. 8029 (SHS);  
01 Civ. 2109 (SHS); 01 Civ. 8177 (SHS)

**DX 3260****Deposition Exhibit**

*Purdue et al. v. Endo et al.*  
Nos. 00 Civ. 8029 (SHS);  
01 Civ. 2109 (SHS); 01 Civ. 8177 (SHS)

**DX 694****P 041765**

6/19/02 GCR

## Unequalled Bioavailability...

■ MS Contin has superior 12-hour bioavailability:

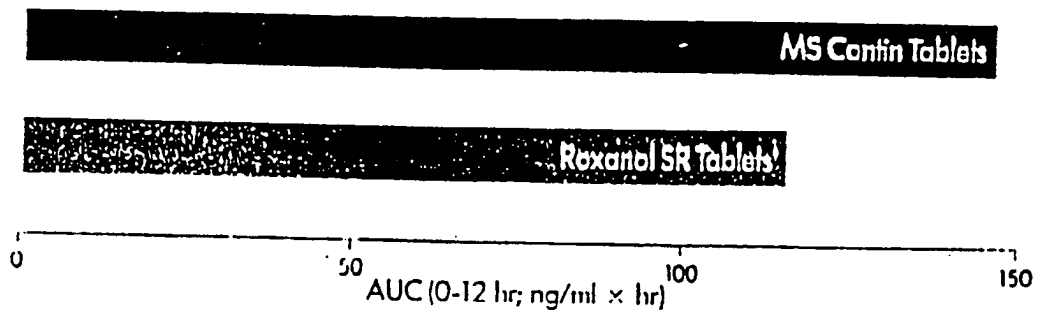
MS Contin is 27% more bioavailable than Roxanol SR.

### Bioavailability:

"The extent to which a drug reaches its site of action or a biological fluid from which the drug has access to its site of action."

(Goldman and Goldman's The Pharmacology of Barbiturates, Edited by Alfred Goldman et al. (7th ed.) New York: Macmillan, 1989, p. 1)

Bioavailability (0-12 hr) of MS Contin 30 mg Tablets vs. Roxanol SR 30 mg Tablets as determined by plasma drug levels in a crossover study in 18 normal volunteers



**Important Note:** While there is an indirect relationship between plasma morphine levels and analgesia, higher plasma levels are generally associated with superior relief of pain, as demonstrated in the literature. There is a lag time or hysteresis between the time of peak plasma morphine levels and the time of peak drug effects.

\*Data based on AUC (0-12 hr) of morphine and its metabolites in plasma.

†MS Contin 30 mg Tablets and Roxanol SR 30 mg Tablets are both formulated with morphine sulfate. The difference in bioavailability is due to the difference in the rate and extent of absorption of the two formulations.

## 12-Hour MS Contin...

# MS Contin<sup>®</sup> (morphine sulfate 30 mg controlled-release) tablets

- No other morphine product is bioequivalent to MS Contin.
- MS Contin and Roxanol SR are not bioequivalent, therefore, Roxanol SR is not therapeutically interchangeable with MS Contin.<sup>1,††</sup>
- MS Contin reaches a significantly higher peak concentration, for more effective analgesia.

## Bioequivalence:

"They [pharmaceutical formulations] are said to be biologically equivalent if they yield similar concentrations of drug in blood and tissues...Pharmaceutical preparations that are chemically equivalent but not biologically or therapeutically equivalent are said to differ in their bioavailability."

Contin and Roxanol, Vol. 1, p. 10

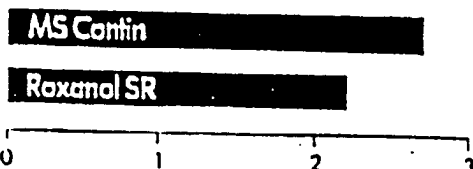
The three criteria for bioequivalency are comparable...

1. bioavailability (calculated from area under the time-concentration-curve)
2. time to peak plasma concentration
3. peak concentration

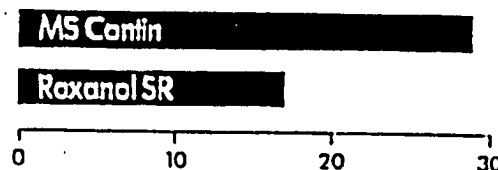
## Results of Comparative Study<sup>1</sup>

|                             | MS Contin<br>(2 x 30 mg)        | Roxanol SR<br>(2 x 30 mg) |
|-----------------------------|---------------------------------|---------------------------|
| AUC                         | 147<br>(0-12 hr;<br>ng/ml x hr) | 116                       |
| T <sub>max</sub><br>(hrs)   | 2.7                             | 2.2                       |
| C <sub>max</sub><br>(ng/ml) | 29                              | 17                        |

Time to Peak Concentration (T<sub>max</sub>)<sup>†</sup>



Peak Concentration (C<sub>max</sub>)<sup>†</sup>



<sup>1</sup> See MS Contin Comparative Bioequivalency of Two Controlled-Release Morphine Tablets. Accepted for presentation at the Sixth Annual Meeting of the American Pain Society, Washington, D.C., Nov. 1988.

<sup>††</sup> See MS Contin Comparative Bioequivalency of Controlled-Release Oral Morphine Tablets for Long- vs. Short-Acting Analgesia. Accepted for presentation at the 38th World Conference on Clinical Pharmacology and Therapeutics, Stockholm, Sweden, September 1988.

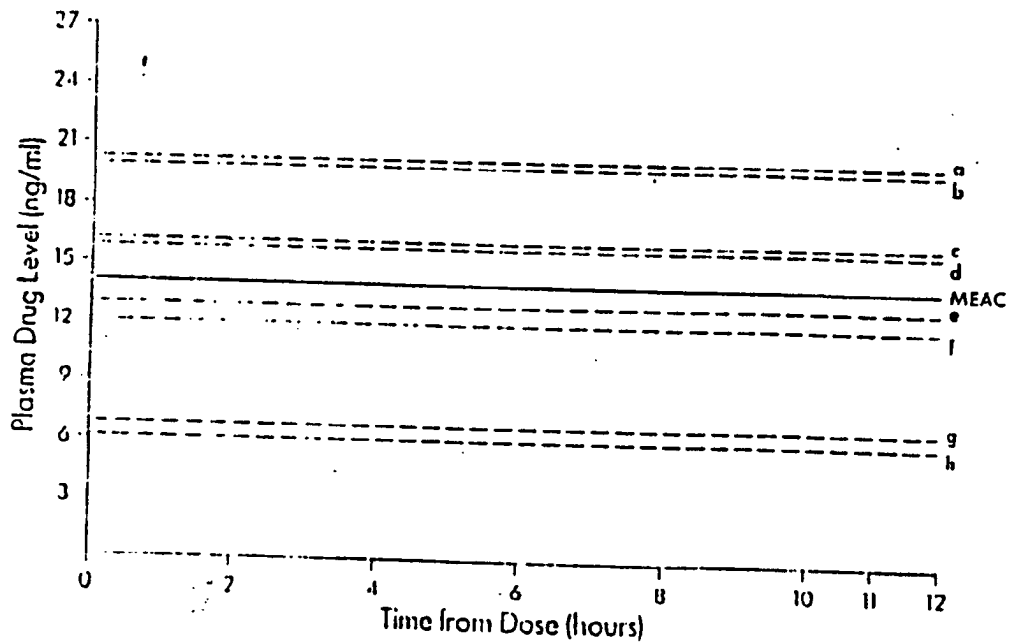
# Proven Against Cancer Pain

# Unequalled Effectiveness...

## What is the effective analgesic level of oral morphine?

A careful review of the literature<sup>a-h</sup> indicates the complexity of defining effective analgesic plasma morphine levels. However, there is generally a "Minimally Effective Analgesic Concentration" (MEAC) of plasma morphine below which no analgesia is provided (see Chart below).

Minimally Effective Analgesic Concentrations (MEAC) of Morphine



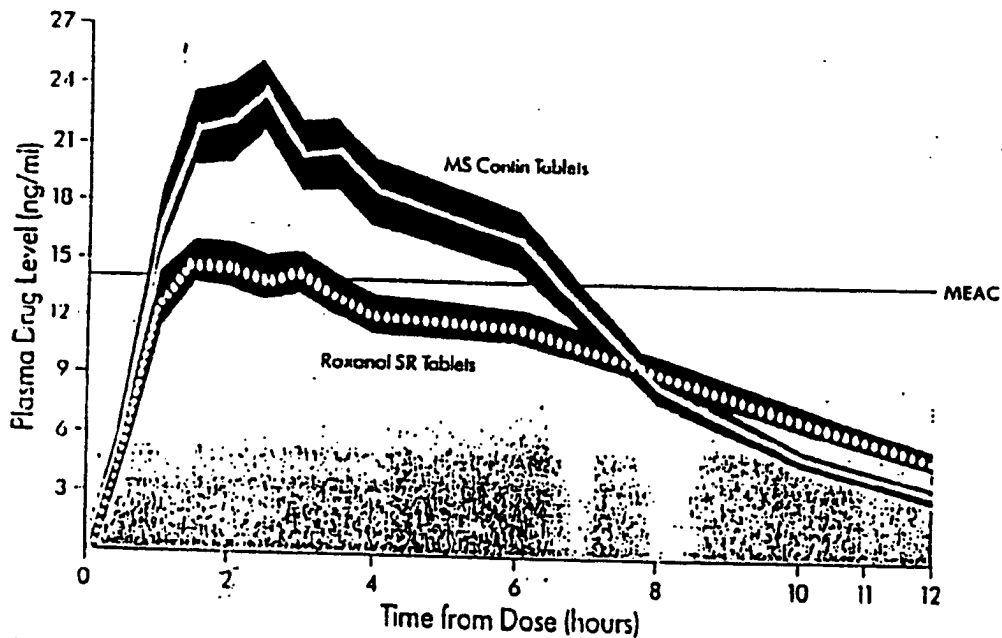
References: a) J. Clin. Pharmacol. 1984; 24: 100-104. b) J. Clin. Pharmacol. 1984; 24: 105-109. c) J. Clin. Pharmacol. 1984; 24: 110-114. d) J. Clin. Pharmacol. 1984; 24: 115-119. e) J. Clin. Pharmacol. 1984; 24: 120-124. f) J. Clin. Pharmacol. 1984; 24: 125-129. g) J. Clin. Pharmacol. 1984; 24: 130-134. h) J. Clin. Pharmacol. 1984; 24: 135-139.

## 12-Hour MS Contin<sup>®</sup>...

## MS Contin<sup>®</sup> (morphine sulfate 30 mg controlled-release) tablets

- MS Contin achieves significantly higher analgesic concentrations.<sup>1,1†</sup>
- MS Contin maintains plasma levels above the minimally effective analgesic concentration (MEAC) significantly longer.

Plasma morphine concentration (mean  $\pm$  SE) following equal doses of MS Contin and Roxanol SR<sup>†</sup>



**Important Notes:** While qualitative differences between morphine formulations are unlikely to vary among subject groups, the absolute magnitude of plasma morphine levels and pharmacokinetic parameters observed here in young normal subjects are likely to be different from those in older subjects and in patients with advanced disease. For example, the apparent plasma morphine elimination half-life can be expected to be prolonged in such patients.

Additionally, there is a lag time, or hysteresis, between the time of peak plasma morphine levels and the time of peak drug effects.<sup>11†</sup>

<sup>1†</sup> See, for example, the results of the 12-hour study of 12 subjects receiving 30 mg of Morphine Tablets. The data are presented in the 12th Annual Meeting of the American Pain Society, Washington, D.C., Nov. 1994. <sup>11†</sup> See, for example, the results of the 12-hour study of 12 subjects receiving 30 mg of Morphine Tablets. The data are presented in the 12th Annual Meeting of the American Pain Society, Washington, D.C., Nov. 1994. <sup>†</sup> See, for example, the results of the 12-hour study of 12 subjects receiving 30 mg of Morphine Tablets. The data are presented in the 12th Annual Meeting of the American Pain Society, Washington, D.C., Nov. 1994.

# Proven Against Cancer Pain

## Unequalled Experience...

- Extensive published clinical documentation that supports 12-hour efficacy and safety<sup>1-14</sup>
- Over 6 years' proven clinical experience with over a half-million prescriptions<sup>1</sup>
- MS Contin has a clinically documented safety profile:  
In over 95% of patients, side effects were fewer or equal to pre-study analgesic<sup>15-17</sup>

Percent of patients experiencing fewer or equal side effects<sup>15-17</sup>

### Study #1: Memorial Sloan-Kettering Cancer Center

55% of patients experienced fewer side effects  
21% of patients experienced equal side effects

### Study #2: New York University School of Medicine

91% of patients experienced fewer side effects  
6% of patients experienced equal side effects

### Study #3: Bowman Gray School of Medicine

52% of patients experienced fewer side effects  
48% of patients experienced equal side effects

117,000 prescriptions reported in clinical pharmacology on LRI (1998-99) and on LSA (1999)

## 12-Hour MS Contin<sup>®</sup>...

# MS Contin<sup>®</sup> (morphine sulfate 30 mg controlled-release) tablets

- **MS Contin is the subject of two international symposia on pain control.<sup>18-19</sup>**
- **Safety and efficacy demonstrated at prestigious cancer treatment centers in over 1200 study patients.**
- **Professional educational support:**  
Speakers' Bureau; Educational Slides and Videotapes, including "Cancer Pain Management" Chaired by Dr. Kathleen M. Foley of Memorial Sloan-Kettering Cancer Center.
- **MS Contin Tablets are small, round and film coated.**  
*Their distinctive lavender color makes them easy to recognize and identify.*  
*Their small size (less than half that of Roxanol SR) makes them easy to swallow.*



References: 1. Harrison et al. and Harrison, J. Controlled evaluation and ongoing trial of continuous subcutaneous morphine in patients with advanced cancer. Presented at the 1982 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1982. 2. Harrison GW and Harrison J. Controlled release morphine tablets are effective in long-term daily dosing relieving severe pain. Presented at the 1982 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1982. 3. Walsh TD. Clinical evaluation of new release morphine tablets. Advances in Pain Research and Therapy 9:727-731, 1985. 4. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 5. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 6. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 7. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 8. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 9. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 10. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 11. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 12. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 13. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 14. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 15. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 16. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 17. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 18. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984. 19. Harrison GW. Clinical trial of continuous subcutaneous morphine tablets and oral morphine tablets in patients with severe pain. Presented at the 1984 International Symposium on Pain Control, Toronto, Canada, September 19-20, 1984.


## Proven Against Cancer Pain


# MS Contin<sup>®</sup> is Unequaled...

The only 12-hour oral narcotic analgesic proven against cancer pain.

- Superior 12-hour bioavailability – 27% more bioavailable than Roxanol SR.
- No other morphine product is bioequivalent to MS Contin; therefore, none is therapeutically interchangeable.
- Achieves a significantly higher peak concentration – for more effective analgesia.
- Maintains plasma morphine levels above the minimally effective analgesic concentration (MEAC) significantly longer – for effective pain relief.
- Published clinical documentation of superior or equal efficacy compared to immediate-release morphine and other oral opioid analgesics.
- Proven safety profile – published clinical documentation shows fewer side effects than previous analgesic (Hydromorphone, Methadone, Oxycodone, Codeine, Meperidine).

Also available

**MSIR<sup>™</sup>** Useful in starting patients on morphine or for treating breakthrough or incident pain.  
(morphine sulfate) 15 mg and 30 mg Immediate-Release Tablets 

**12-hour MS Contin<sup>®</sup>**   
(morphine sulfate 30 mg controlled-release) tablets  
**Proven Against Cancer Pain**

For Prescribing Information Please See Accompanying Professional Literature

Purdue Frederick Copyright 1986, 1987, The Purdue Frederick Company, Norwalk, CT 06856 82143 PM28

P 041772



Respiratory distress may occur in newborns who have received morphine during labor. A specific monitoring protocol, including, but not limited to, respiratory depression, should be available for reversal of neonatal respiratory depression in the neonate.

#### Nursing Mothers

The use of morphine has been detected in the breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine is stopped. Ordinarily, nursing should not be undertaken until a patient is receiving MS CONTIN pain morphine may be resumed on the milk.

#### Pregnant Use

MS CONTIN has not been evaluated systematically in children.

#### ADVERSE REACTIONS

The adverse or untoward effects caused by morphine are described below under each of the following categories. They include the following major adverse effects: respiratory depression, nausea, and to a lesser degree, constipation, depression, respiratory arrest, shock and cardiac arrest.

#### Most Frequently Observed

Constipation, sedation/drowsiness, dizziness, depression, nausea, vomiting, sweating, dyspnea and euphoria.

Some of these effects tend to be more pronounced in ambulatory patients and in those not receiving severe pain. Some adverse reactions in ambulatory patients may be alleviated if the patient has eaten.

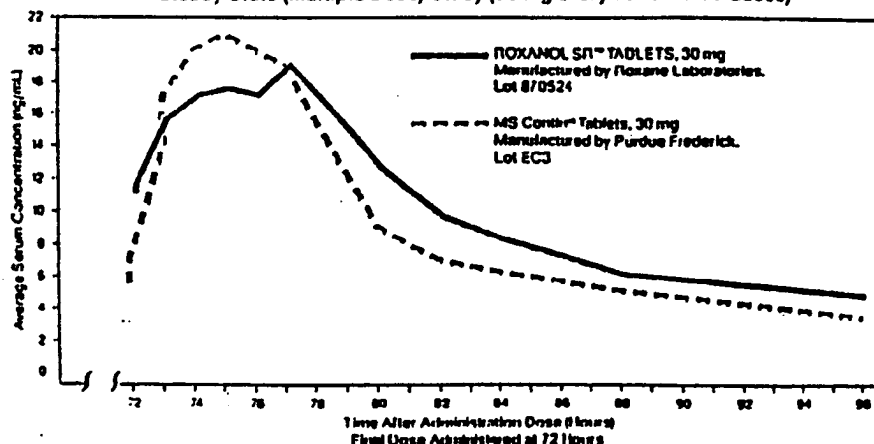
#### Less Frequently Observed Reactions

(From the *Journal of Clinical Pharmacology*, 1978; 18: 100-101, 102-103, 104-105, 106-107, 108-109, 110-111, 112-113, 114-115, 116-117, 118-119, 120-121, 122-123, 124-125, 126-127, 128-129, 130-131, 132-133, 134-135, 136-137, 138-139, 140-141, 142-143, 144-145, 146-147, 148-149, 150-151, 152-153, 154-155, 156-157, 158-159, 160-161, 162-163, 164-165, 166-167, 168-169, 170-171, 172-173, 174-175, 176-177, 178-179, 180-181, 182-183, 184-185, 186-187, 188-189, 190-191, 192-193, 194-195, 196-197, 198-199, 200-201, 202-203, 204-205, 206-207, 208-209, 210-211, 212-213, 214-215, 216-217, 218-219, 220-221, 222-223, 224-225, 226-227, 228-229, 230-231, 232-233, 234-235, 236-237, 238-239, 240-241, 242-243, 244-245, 246-247, 248-249, 250-251, 252-253, 254-255, 256-257, 258-259, 260-261, 262-263, 264-265, 266-267, 268-269, 270-271, 272-273, 274-275, 276-277, 278-279, 280-281, 282-283, 284-285, 286-287, 288-289, 290-291, 292-293, 294-295, 296-297, 298-299, 300-301, 302-303, 304-305, 306-307, 308-309, 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**AVERAGE SERUM CONCENTRATIONS OF  
MORPHINE FOR ROXANOL SR™ TABLETS AND MS CONTIN® TABLETS**  
Steady State (Multiple Dose) Study (30 mg every 12 hours x 7 doses)



Time After Administration (hours)  
Final Dose Administered at 72 hours  
Adapted from Abstracts of the 1988 American Society of Clinical Oncologists Meeting

Multiple-dose randomized crossover trial  
demonstrates Roxanol SR and MS Contin  
are bioequivalent.

□ Evaluations of standard pharmacokinetic parameters (AUC 72-96 hr, AUC 72-84 hr, C<sub>max</sub> and C<sub>avg</sub>) showed less than 10% difference between the two sustained release morphine treatments.

□ The investigators concluded that Roxanol SR is bioequivalent to MS Contin.

**More cost-effective  
than MS Contin**

□ Roxanol SR offers greater cost containment benefits for hospitals.\*

□ Roxanol SR is a greater value for patients who need relief of chronic cancer pain.\*

\*Based on 1988 National Survey

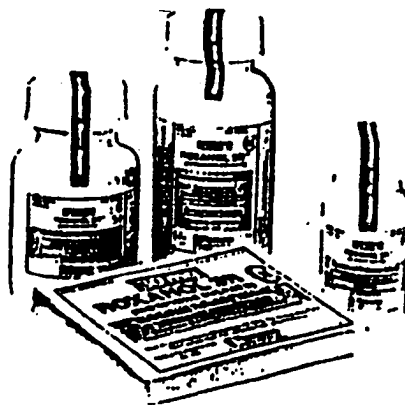
**ROXANOL SR™ Tablets @**  
**(Morphine Sulfate Sustained Release Tablets)**

WARNING: May be habit forming.

## Dosing and Administration

The patients should first be stabilized on Roxanol Concentrated Oral Solution. Convert to Roxanol SR by dividing the total daily Roxanol requirement (in milligrams) by three and administering as Roxanol SR Tablets every eight hours. The dose and dosage schedule can be adjusted for greater flexibility according to severity of pain as well as for the patient's underlying disease, age, and size.

**Tablets must be swallowed whole...not broken, crushed, or chewed. Tablets have a methyl cellulose coating for easier swallowing.**

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